Rising Sun Communications

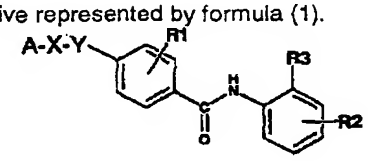
J11-269146
(unexamined)

CAUTION Post-Edited
Machine Translation

Title of the Invention
Differentiation induction agent

(Abstract)
(the subject)
It is to put forward novel benzamide derivative having differentiation induction action.

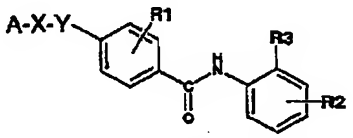
(Method of Solution)
Novel benzamide derivative represented by formula (1).



(1)

(effect)
Because novel benzamides of this invention has differentiation induction action, it is useful as therapy and/or improvement agent for malignant tumour, autoimmune disease, dermatopathia, parasite infestation. In particular it is highly effective as carcinostatic and is effective in hematopoietic organ tumour, solid cancer.

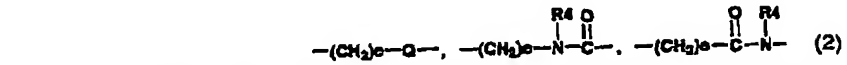
Patent Claims.
(Claim 1)
A benzamide derivative represented by formula (1) or the pharmacologically permitted salt



(1)

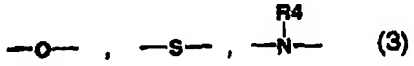
[In the formula, A denotes optionally substituted phenyl group or heterocycle (containing as the substituent, 1-4 groups selected from the group comprising halogen atom, hydroxy group, amino group, nitro group, cyano group, alkyl group of carbon number 1-4, alkoxy group of carbon number 1-4, amino alkyl group of carbon number 1-4, alkylamino group of carbon number 1-4, acyl group of carbon number 1-4, acylimino-group of carbon number 1-4, alkylthio group of carbon number 1-4, perfluoro alkyl group of carbon number 1-4, perfluoro alkyloxy group of carbon number 1-4, carboxyl group, alkoxycarbonyl group of

carbon number 1-4, phenyl group, heterocycle), X denotes any of directly bonding or the structure represented by the formula (2)



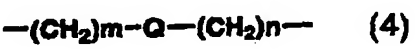
(2)

(In the formula, e denotes an integer of 0-4, and R4 denotes hydrogen atom or alkyl group of carbon number 1-4 that may be substituted), Q denotes any of structure represented by formula (3)



(3)

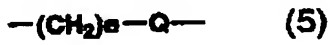
(In the formula, R4 has the same said meanings)}, Y denotes structure represented by formula (4)



(4)

(In the formula, m denotes an integer of 1-4, and Q has the same aforesaid meanings, and n denotes an integer of 0-4), R1 and R2 respectively independently denote hydrogen atom, halogen atom, hydroxy group, amino group, alkyl group of carbon number 1-4, alkoxy group of carbon number 1-4, amino alkyl group of carbon number 1-4, alkylamino group of carbon number 1-4, acyl group of carbon number 1-4, acylimino-group of carbon number 1-4, alkylthio group of carbon number 1-4, perfluoro alkyl group of carbon number 1-4, perfluoro alkyloxy group of carbon number 1-4, carboxyl group or alkoxycarbonyl group of carbon number 1-4 and R3 denotes amino group or hydroxy group.]

(Claim 2)
A benzamide derivative or a pharmacologically acceptable salt thereof in accordance with Claim 1, wherein X comprises any of structure represented by formula (5).



(5)

(In the formula, e and Q have the same said meanings.)

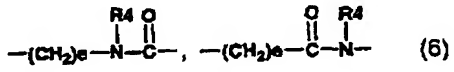
(Claim 3)
A benzamide derivative or a pharmacologically acceptable salt thereof in accordance with Claim 2, wherein A comprises optionally substituted heterocycle.

(Claim 4)
A benzamide derivative or a pharmacologically acceptable salt thereof in accordance with Claim 3, wherein A comprises optionally substituted pyridyl group.

(Claim 5)
A benzamide derivative or a pharmacologically acceptable salt thereof in accordance with Claim 4, wherein R1 and R2 comprise hydrogen atoms.

(Claim 6)
A benzamide derivative or a pharmacologically acceptable salt thereof in accordance with Claim 5, wherein R3 comprises amino group.

(Claim 7)
A benzamide derivative or a pharmacologically acceptable salt thereof in accordance with Claim 1, wherein X comprises any of structure represented by formula (6).



(6)

(In the formula, e and R4 have the same said meanings.)

(Claim 8)
A benzamide derivative or a pharmacologically acceptable salt thereof in accordance with Claim 7, wherein A comprises optionally substituted heterocycle.

(Claim 9)
A benzamide derivative or a pharmacologically acceptable salt thereof in accordance with Claim 8, wherein A comprises optionally substituted pyridyl group.

(Claim 10)
A benzamide derivative or a pharmacologically acceptable salt thereof in accordance with Claim 9, wherein R1 and R2 comprise hydrogen atoms.

(Claim 11)
A benzamide derivative or a pharmacologically acceptable salt thereof in accordance with Claim 10, wherein R3 comprises amino group.

(Claim 12)
A carcinostatic containing one or more compounds in accordance with any of Claims 1-11 as effective ingredient.

(Claim 13)
A drug c containing one or more compounds in accordance with any of Claims 1-11 as effective ingredient.

Detailed Description of the Invention

(0001)
(Technical Sphere of this Invention)
This invention is related to differentiation induction drug. More particularly this invention relates to the use of carcinostatic and other drugs on the basis of differentiation induction action of novel benzamide derivative.

(0002)
(Technology of the Prior Art)
Presently among the causes of death, cancer is the highest cause exceeding cardiac disease, cerebral blood vessel diseases, and so far many studies have been carried out with application of a large amount of cost and time. However, despite the wide ranging study for therapy methods such as surgical operation, radiotherapy, thermotherapy and the like, cancer has not yet ben overcome. Among these, chemotherapy is a large pillar of cancer therapy, but a sufficiently satisfactory drug has not been found, and carcinostatics with high therapy effect and low toxicity are strongly desired. Many carcinostatics in the past gave injury to cancer cells by action on the cells, mainly on DNA, and expressed cytotoxicity, and a carcinostatic effect was displayed. However, because the selectivity for cancer cells over normal cell was not adequate, the side effects occuring in normal cell formed limits for therapy.

(0003)
However, among the carcinostatics, differentiation induction drugs have the object of inducing differentiation of the cancer cells, and suppressing the infinite proliferation of cancer cells instead of directly killing the cells. Therefore although it is not as effective as the direct killing cell types of carcinostatics, a low toxicity and different selectivity are expected in the retraction of cancer. Actually, it is known well that retinoic acid which is a differentiation induction drug is used in therapy, and high effects are demonstrated in acute promyelocytic leukaemia (Huang et al.; Blood, vol. 72, 567-572 (1988), Castaign et al., Blood, vol. 76, 1704-1709 (1990), Warrell et al., New Engl. J. Med. vol. 324, 1385-1393 (1991) and the like). Moreover because vitamin D derivatives demonstrate a differentiation induction action, application as carcinostatics has also been much studied (Olsson et al.; Cancer Res vol. 43, 5862-5867 (1983) and others).

(0004)
These study have been received, and applications of vitamin D derivative which is differentiation induction drug (Tokkai 6-179622), isoprene derivative (Tokkai 6-192073), tocopherol (Tokkai 6-256181), quinone derivative (Tokkai 6-305955), non cyclic poly isoprenoid (Tokkai 6-316520), benzoic acid derivative (Tokkai 7-206765), carcinostatic glycolipid (Tokkai 7-258100) have been reported. However there is not a drug which reaches a sufficient level for a cancer curative even in these studies, and an effective drug against various cancers of high safety is strongly desired.

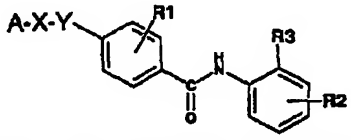
(0005)
Problems to be Overcome by this Invention
The object of this invention is to put forward a compound having differentiation induction action and which is useful as a drug such as a therapy and/or improvement drug for malignant tumour, autoimmune disease, dermatopathia and parasite infestations.

(0006)
The object of this invention is to put forward a novel benzamide derivative, a carcinostatic containing said derivative and a drug containing said derivative.
(0007)
Means to Overcome these Problems

These inventors carried out assiduous investigations to solve these problems, and as a result discovered that the novel benzamide derivative having differentiation induction action demonstrated antitumour effect. This invention was completed on the basis of this discovery.

In other words this invention comprises [1] a benzamide derivative or a pharmacologically acceptable salt thereof represented by formula (1)

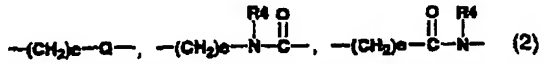
(0008)



(1)

[In the formula, A denotes optionally substituted phenyl group or heterocycle (containing as the substituent 1-4 groups selected from the group comprising halogen atom, hydroxy group, amino group, nitro group, cyano group, alkyl group of carbon number 1-4, alkoxy group of carbon number 1-4, amino alkyl group of carbon number 1-4, alkylamino group of carbon number 1-4, acyl group of carbon number 1-4, acylimino-group of carbon number 1-4, alkylthio group of carbon number 1-4, perfluoro alkyl group of carbon number 1-4, perfluoro alkyloxy group of carbon number 1-4, carboxyl group, alkoxycarbonyl group of carbon number 1-4, phenyl group, heterocycle), X denotes any of directly bonding or the structure represented by the formula (2)

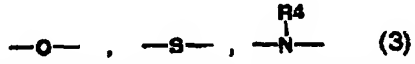
(0009)



(2)

{In the formula, e denotes an integer of 0-4, and R4 denotes hydrogen atom or alkyl group of carbon number 1-4 that may be substituted, Q denotes any of structure represented by formula (3)

(0010)



(3)

(In the formula, wherein, R4 has the same said meanings)}, Y denotes structure represented by formula (4)

(0011)

$$-(CH_2)m-Q-(CH_2)n- \quad (4)$$

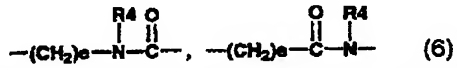
(In the formula, m denotes an integer of 1-4, and Q has the same aforesaid meaning, and n denotes an integer of 0-4), R1 and R2 respectively independently denote hydrogen atom, halogen atom, hydroxy group, amino group, alkyl group of carbon number 1-4, alkoxy group of carbon number 1-4, amino alkyl group of carbon number 1-4, alkylamino group of carbon number 1-4, acyl group of carbon number 1-4, acylimino-group of carbon number 1-4, alkylthio group of carbon number 1-4, perfluoro alkyl group of carbon number 1-4, perfluoro alkyloxy group of carbon number 1-4, carboxyl group or alkoxycarbonyl group of carbon number 1-4 and R3 denotes amino group or hydroxy group, or [2] a benzamide derivative or a pharmacologically acceptable salt thereof in accordance with [1], wherein X comprises any of structure represented by formula (5)

(0012)

$$-(CH_2)e-Q- \quad (5)$$

(In the formula, e and Q have the same said meanings), or [3] a benzamide derivative or a pharmacologically acceptable salt thereof in accordance with [2], wherein A comprises optionally substituted heterocycle, or [4] a benzamide derivative or a pharmacologically acceptable salt thereof in accordance with the [3], wherein A comprises optionally substituted pyridyl group, or [5] a benzamide derivative or a pharmacologically acceptable salt thereof in accordance with [4], wherein R1 and R2 comprise hydrogen atoms, or [6] a benzamide derivative or a pharmacologically acceptable salt thereof in accordance with [5], wherein R3 comprises amino group, or [7] a benzamide derivative or a pharmacologically acceptable salt thereof in accordance with [1], wherein X comprises any of structure represented by formula (6)

(0013)



(6)

(In the formula, e and R4 have the same said meanings), or [8] a benzamide derivative or a pharmacologically acceptable salt thereof in accordance with [7], wherein A comprises optionally substituted heterocycle, or [9] a benzamide derivative or a pharmacologically acceptable salt thereof in accordance with Claim 8, wherein A comprises optionally substituted pyridyl group, or [10] a benzamide derivative or a pharmacologically acceptable

salt thereof in accordance with [9], wherein R1 and R2 comprise hydrogen atoms, or [11] a benzamide derivative or a pharmacologically acceptable salt thereof in accordance with [10], wherein R3 comprises amino group, or [12] a carcinostatic containing one or more compounds in accordance with any of [1]-[11] as effective ingredient and moreover, [13] a drug comprising containing one or more compounds in accordance with any of [1]-[11] as effective ingredient.

(0014)
Conditions for carrying out this invention
Below, this invention is described in greater detail. As carbon number 1-4 stated in this invention, the carbon number per the unit substituent is denoted. In other words, in case of for example dialkyl substitution the carbon number 2-8 is denoted.

(0015)
The heterocycle in the compound represented by formula (1) comprises monocyclic heterocycle or bicyclic condensed heterocycle comprising 5 membered ring or 6 membered ring containing 1-4 sulphur atom, oxygen atom or nitrogen atom, and as monocyclic heterocycle, for example pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, pyrrole, pyrazole, isooxazole, isothiazole, imidazole, oxazole, thiazole, piperidine, piperazine, pyrrolidine, quinacridine, tetrahydrofuran, morpholine, thiomorpholine and the like are nominated and as bicyclic condensed heterocycle, for example condensed pyridine ring such as quinoline, isoquinoline, naphthyridine, furopyridine, thienopyridine, pyrrolopyridine, oxazolo pyridine, imidazolo pyridine, thiazolopyridine and the like, benzofuran, benzo thiophene, benzimidazole and the like are nominated.

(0016)
As halogen atom, fluorine atom, chlorine atom, bromine atom and iodine atom are nominated.

(0017)
As alkyl group of carbon number 1-4, for example methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, t-butyl group are nominated.

(0018)
As alkoxy group of carbon number 1-4, for example methoxy group, ethoxy group, n-propoxy group, isopropoxy group, allyloxy group, n-butoxy group, isobutoxy group, sec-butoxy group, t-butoxy group are nominated. As amino alkyl group of carbon number 1-4, for example aminomethyl group, 1-amino ethyl group, 2-aminopropyl group are nominated.

(0019)
As alkylamino group of carbon number 1-4, for example N-methylamino group, N,N-dimethylamino function, N,N-diethylamino group, N-methyl-N-ethylamino group, N,N-diisopropylamino group are nominated.

(0020)
As acyl group of carbon number 1-4, for example acetyl group, propanoyl group, butanoyl group are nominated.

(0021)
As acylamino-group of carbon number 1-4, for example acetylamino group, propanoyl amino group, butanoyl amino groups are nominated.

(0022)
As alkylthio group of carbon number 1-4, methylthio group, ethylthio group, propylthio group are nominated.

(0023)
As perfluoro alkyl group of carbon number 1-4, for example trifluoromethyl group, pentafluoro ethyl groups are nominated.

(0024)
As perfluoro alkyloxy group of carbon number 1-4, for example trifluoro methoxy group, pentafluoro ethoxy group are nominated.

(0025)
As alkoxycarbonyl group of carbon number 1-4, for example methoxycarbonyl group, ethoxycarbonyl group are nominated.

(0026)
As alkyl group of carbon number 1-4 that may be substituted, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, t-butyl group and the like, and the one having as the substituent thereof 1-4 groups selected from the group comprising halogen atom, hydroxy group, amino group, nitro group, cyano group, phenyl group, heterocycle.

(0027)
As a salt of the pharmacologically permitted compound, salt of inorganic acid such as hydrochloric acid, hydrobromic acid, sulphuric acid, orthophosphoric acid and the like which are used regularly in this sphere, and salt of organic acid such as acetic acid, lactic acid, tartaric acid, malic acid, succinic acid, fumaric acid, maleic acid, citric acid, benzoic acid, trifluoroacetic acid, p-toluenesulphonic acid, methanesulphonic acid and the like can be nominated.

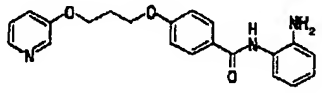
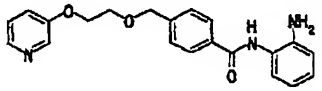
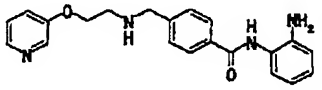
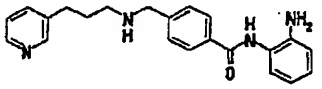
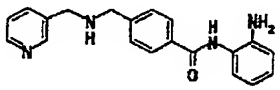
(0028)
The drug denotes therapy and/or improvement drug for autoimmune disease, dermatopathia, parasite infestation in addition to carcinostatic.

(0029)
When the compound represented by formula (1) contains asymmetric carbon, it can be present in a form of mixture of stereoisomerism form including different stereoisomerism forms or the racemic form. In other words this invention includes various kinds of forms prescribed like these, but these can be used as the effective ingredient compound in the same way.

(0030)
Hereinafter typical compounds represented by formula (1) of this invention are exemplified in Table-1 (Table 1-Table 10). Moreover this invention is not restricted to these examples.

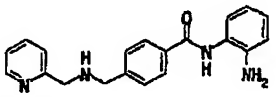
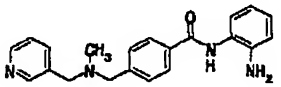
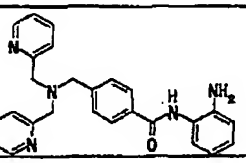
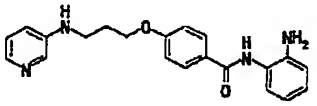
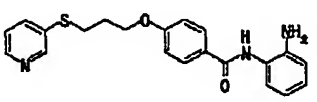
(0031)
(Table 1)

TABLE-1-1

Compound No.	Structural formula
1	
2	
3	
4	
5	

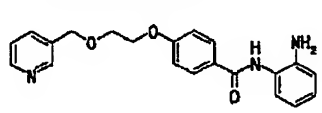
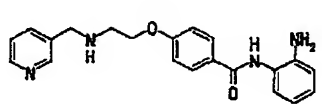
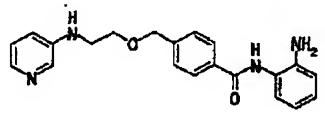
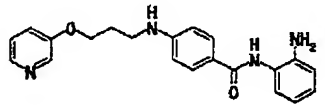
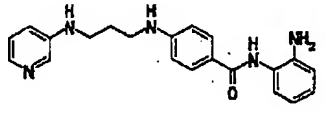
(0032)
(Table 2)

TABLE-1-2

Compound No.	Structural formula
6	
7	
8	
9	
10	

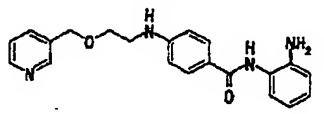
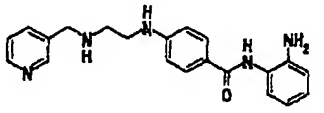
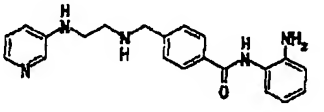
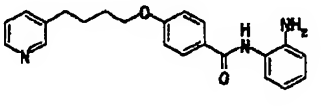
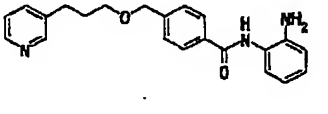
(0033)
(Table 3)

TABLE-1-3

Compound No.	Structural formula
11	
12	
13	
14	
15	

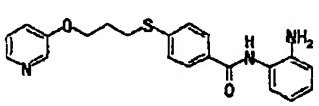
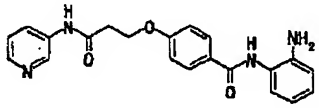
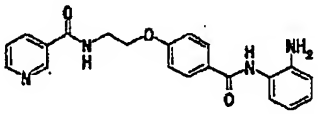
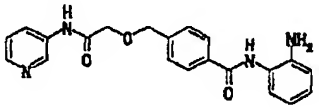
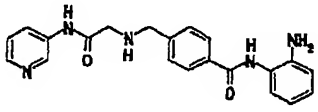
(0034)
(Table 4)

TABLE-1-4

Compound No.	Structural formula
16	
17	
18	
19	
20	

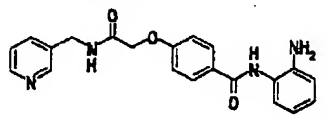
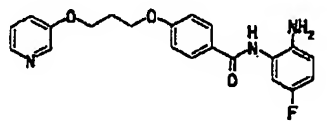
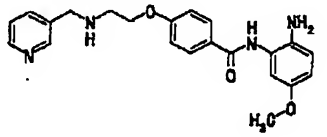
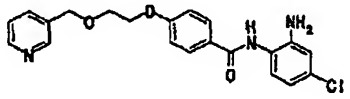
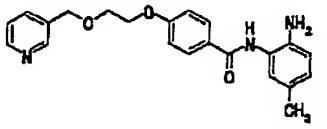
(0035)
(Table 5)

TABLE-1-5

Compound No.	Structural formula
21	
22	
23	
24	
25	

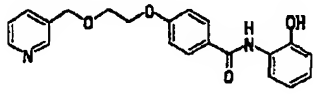
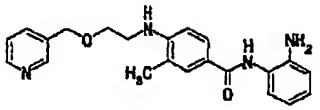
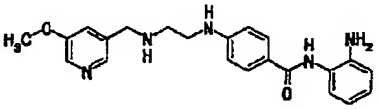
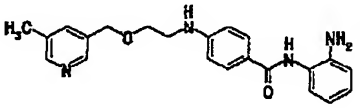
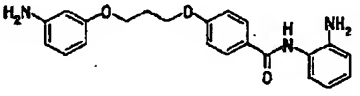
(0036)
(table 6)

TABLE-1-6

Compound No.	Structural formula
26	
27	
28	
29	
30	

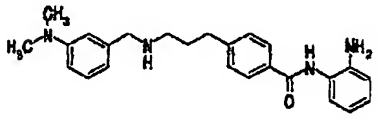
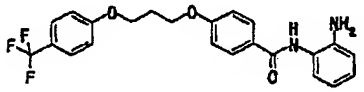
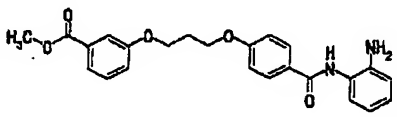
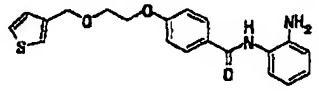
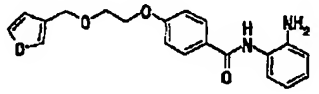
(0037)
(table 7)

TABLE-1-7

Compound No.	Structural formula
31	
32	
33	
34	
35	

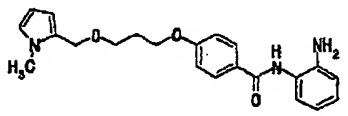
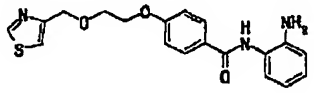
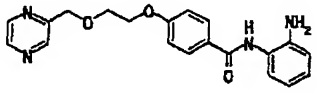
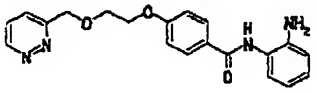
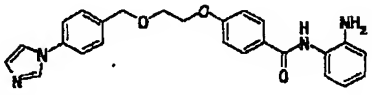
(0038)
(Table 8)

TABLE-1-8

Compound No.	Structural formula
36	
37	
38	
39	
40	

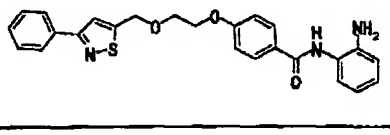
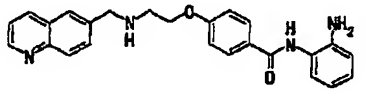
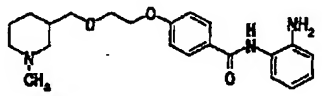
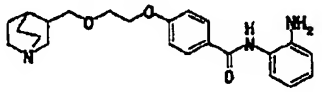
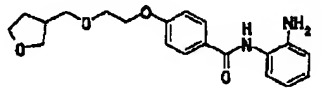
(0039)
(table 9)

TABLE-1-9

Compound No.	Structural formula
41	
42	
43	
44	
45	

(0040)
(table 10)

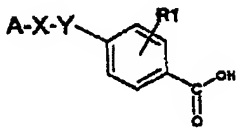
TABLE-1-10

Compound No.	Structural formula
46	
47	
48	
49	
50	

The compound of this invention is able to be produced for example by the process as follows.

[a] The compound of this invention can be produced by subjecting the compound represented by formula (7)

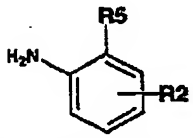
(0041)



(7)

(in the formula, A, X, Y and R1 have the same said meanings) and the compound represented by formula (8)

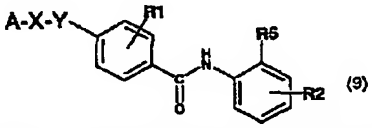
(0042)



(8)

(in the formula, R2 has the same said meanings, and R5 denotes amino group protected with protecting group used in ordinary peptide forming reaction such as t-butoxycarbonyl group or hydroxy group protected with protecting group used in ordinary peptide forming reaction such as benzyl group) to condensation reaction, and by eliminating protecting group of the thereby obtained compound represented by formula (9)

(0043)

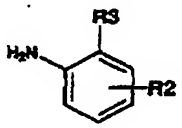


(9)

(in the formula, A, X, Y, R1, R2 and R5 have the same said meanings).

[b] The compound of this invention can be produced by condensation reaction of the compound represented by formula (7) and the compound represented by formula (10)

(0044)



(10)

(In the formula, R2 and R3 has the same said meanings).

(0045)

Condensation reaction of [a] and [b] can be put into effect by ordinary amide bond forming reaction for peptide, for example process of active ester or mixed acid anhydride or acid chloride. For example, the compound represented by formula (7) and phenols such as 2,4,5-trichlorophenol, pentachlorophenol or 4-nitrophenol and the like or N-hydroxy compound such as N-hydroxysuccinimide, N-hydroxybenzotriazole and the like are condensed in the presence of dicyclohexylcarbodiimide, thereby it is converted into active ester, and thereafter it can be carried out by condensation with amine component [the compound represented by formula (8) or the compound represented by formula (10)].

(0046)
Moreover, it can be carried out by reacting carboxylic acid component [the compound represented by formula (7)] with oxalyl chloride, thionyl chloride, phosphorus oxychlorides and the like, thereby converting into acid chloride, and thereafter condensing with amine component [the compound represented by formula (8) or the compound represented by formula (10)].

(0047)
Moreover, it can be carried out by reacting carboxylic acid component [the compound represented by formula (7)] isobutyl chlorocarbonate, methanesulphonyl chloride or p-nitrobenzene sulphonyl chloride and the like, thereby obtaining mixed acid anhydride, and thereafter condensing with amine component [the compound represented by formula (8) or the compound represented by formula (10)].

(0048)
Furthermore, aforesaid condensation reaction can be carried out by using peptide condensation reagent alone such as dicyclohexylcarbodiimide, N,N-carbonyldiimidazole, diphenyl phosphoric acid azide, diethyl phosphoric acid cyanide, 2-chloro-1,3-dimethyl imidazoloninum chloride and the like.

(0049)
The reaction is carried out at -20 to +50 degrees usually for 30 minutes to 48 hours. As the solvent used, for example, alcohols such as methanol, ethanol and the like or a mixture thereof are nominated in addition to aromatic hydrocarbon species such as benzene, toluene and the like, ethers such as tetrahydrofuran, dioxane, diethyl ether and the like,

halogenated hydrocarbons such as methylene chloride, chloroform and the like, N,N-dimethylformamide. In accordance with requirements organic base for example triethylamine or pyridine is added and is reacted.

(0050)
Elimination of protecting groups of the compound represented by formula (9) is performed under conditions to be used in ordinary peptide forming reaction. For example, when R5 is an amino group protected with t-butoxycarbonyl group in formula (9), deprotecting reaction can be carried out by treating with acid such as hydrochloric acid or trifluoroacetic acid.

(0051)
Salt of the compound represented by formula (1) can be obtained by reaction to produce compound represented by formula (1), but the salt can be easily formed with pharmacologically acceptable acid. As acid thereof, for example inorganic acid such as hydrochloric acid, hydrobromic acid, sulphuric acid, orthophosphoric acid and organic acid such as acetic acid, tartaric acid, fumaric acid, maleic acid, citric acid, benzoic acid, trifluoroacetic acid, p-toluenesulphonic acid are nominated. These salts can also be used as the effective ingredient compound of this invention in the same way as in the free form of the compound of formula (1).

(0052)
The compound represented by formula (1) can be isolated and purified from the reaction mixture by ordinary separation means, for example process such as extraction, recrystallisation method, column chromatography.

(0053)
Novel benzamides of this invention have differentiation induction action and are useful as therapy and/or improvement agent for malignant tumour, autoimmune disease, dermatopathia, parasite infestation. Wherein, as malignant tumour, in addition to hematopoietic organ tumours such as acute leukaemia, chronic leukaemia, malignancy lymphoma, multiple myeloma, macroglobulinemia, solid tumours such as colon cancer, brain tumour, head cervix cancer, breast cancer, lung cancer, cancer of the esophagus, gastric cancer, hepatoma, gallbladder cancer, bile duct cancer, pancreatic carcinoma, insula pancreatica cell cancer, kidney cell cancer, adrenal cortex cancer, tumour of the

urinary bladder, prostatic cancer, testis tumour, ovary cancer, uterine cancer, carcinoma villosum, cancer of the thyroid, bad carcinoid tumour, skin cancer, malignant melanoma, osteosarcoma, soft tissue sarcoma, neuroblastoma, Wilms tumour, retinoblastoma are nominated. As autoimmune disease, rheumatism, nephritis, diabetes mellitus, systemic lupus erythematosus, human autoimmune lymphocytotic lymphadenopathy, immunoblastic lymphadenopathy, Crohn's disease, ulcerative colitis are nominated. As dermatopathia, psoriasis, acne, eczema, atopic dermatitis, parasitic dermatosis, alopecia, pyogenic dermatosis, skin sclerosis are nominated. As parasite infestation, a disease caused by infection of parasite such as malaria infection is denoted. Moreover target disease of this invention does not need to be restricted to these.

(0054)
The effective ingredient compounds of this invention are useful as drug, and these are used in a form of general medical formulation. Formulation is prepared using diluent of for example filler, expander, binding agent, moisturising agent, disintegrating agent, surface active agent, lubricant or excipient which are usually used. As this drug formulation, various forms can be selected corresponding to the therapy object and as representative thereof, tablet, pill, powder, liquid medicine, suspending agent, emulsion, granule, capsule agent, injection (liquid medicine, suspending agent) and suppository and the like are nominated.

(0055)
When it is formed into a tablet, various ones which is known well in the prior art as a carrier in this sphere, can be widely used. As example thereof, for example excipient such as lactose, dextrose, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid, and the like, binding agent such as water, ethanol, propyl alcohol, single syrup, dextrose liquid, starch liquid, gelatine solution, carboxymethyl cellulose, shellac, methyl cellulose, polyvinylpyrrolidone and the like, disintegrating agent such as dried starch, sodium alginate, agar powder, carmellose calcium, starch, lactose, disintegration depressant such as refined sugar, cacao butter, hydrogenation oil, absorption promoter such as quaternary ammonium salt group, sodium lauryl sulphate and the like, moisturising agent such as glycerine, starch and the like, adsorbent such as starch, lactose, kaolin, bentonite, colloidal silicic acid, lubricant such as talc, stearate, polyethyleneglycol and the like can be used. Furthermore, as for a tablet, it can be made into coated tablet of ordinary agent in accordance with

requirements, for example sugar coated tablet, gelatine encapsulation tablet, enteric-coated encapsulation tablet, film coating tablet or bilayer tablet, multilayer tablet.

(0056)
When it is formed into pill, ones well known in prior art in this sphere as a carrier, can be widely used. As example thereof, for example excipients such as crystalline cellulose, lactose, starch, hardening vegetable oil, kaolin, talc and the like, binding agent such as powdered gum Arabic, tragacanth powder, gelatine and the like, disintegrating agent such as carmellose calcium, agar and the like are nominated.

(0057)
Capsule agent is prepared by mixing the effective ingredient compound with above-mentioned various carriers according to conventional method, and packing into hard gelatine capsule, soft capsule and the like.

(0058)
When it is prepared as injection, it is preferred that liquid medicine, emulsion and suspending agent are sterilised and are isotonic with blood, and when it is formed into these, ones conventionally used in prior art in this sphere as diluent, for example water, ethanol, macrogol, propylene glycol, ethoxylation isostearyl alcohol, polyoxyisosteary alcohol, polyoxyethylene sorbitan fatty acid ester species can be used. In this case, sodium chloride, dextrose or glycerine of necessary quantity may be contained in drug formulation to prepare an isotonic solution, and moreover ordinary solubiliser, buffer agent, analgesic and the like may be added.

(0059)
When it is formed into suppository, ones well known in prior art as a carrier can be widely used. As example thereof, for example semi-synthetic glyceride, cacao butter, esters of higher alcohol, higher alcohol, polyethyleneglycol and the like are nominated.

(0060)
Furthermore colorant, preservative, flavour, flavour agent, sweetener and other drug can be contained in the drug formulation in accordance with requirements.

(0061)
The quantity of the effective ingredient compound which should be contained in these drug formulations of this invention is not restricted in particular and suitably selected from a wide range, but it is usually about 1-70 wt.% and preferably made into about 5-50 wt.% in the formulation composition.

(0062)
As for the administration method of these drug formulation of this invention, there are no restrictions in particular and it is administered by the methods that suits various formulation, age of patient, sex, degree of disease and other conditions. For example, in the cases of tablet, pill, liquid medicine, suspending agent, emulsion, granule and capsule agent, it is orally-administered, and in the case of injection, it is administered intravenously by itself or by being mixed with ordinary fluid replacement such as glucose, amino acid, and furthermore it is administered intramuscularly, subcutaneously or intraperitoneously by itself in accordance with requirements. In the case of suppository, it is administered in rectum.

(0063)
Dosage of these drug formulation of this invention is suitably selected by application, age of patient, sex, degree of disease and other conditions, but it is usually made into about around 0.0001-100 mg as the quantity of the effective ingredient compound per day per 1 kg weight. Moreover, it is desirable that the effective ingredient compound is contained by about 0.001-1,000 mg range in the formulation of administration unit form.

(0064)
The compound and salts thereof represented by formula (1) of this invention do not demonstrate toxicity in dosage that demonstrates pharmacological effect.

(0065)
(Example)
Below this invention is described in greater detail with Examples, but this invention is not restricted to these. Moreover number in brackets of title is the number of the compound exemplified in Detailed Description.

(0066)

Example 1.
Synthesis of N-(2-aminophenyl)-4-[3-(pyridine-3-yloxy) propoxy] benzamide (Table-1: compound number 1).

(1-1) Diethyl azodicarboxylate ester 1.1 g (6 mmol) was added to THF (20 ml) solution of 4-hydroxybenzoic acid ethyl ester 1.0 g (6 mmol), 3-bromo propanol 0.84 g (6 mmol), triphenylphosphine 1.6 g (6 mmol), and was stirred for one hour. The reaction mixture was concentrated, thereafter distributed between ethyl acetate and water. Organic layer was dried with anhydrous magnesium sulphate, and next concentrated and refined by silica gel column chromatography (solvent, hexane : ethyl acetate = 9:1), and 4-(3-bromo propoxy) ethyl benzoate 1.1 g (yield 63 %) was obtained as a colourless oily substance.
1H NMR (270 M Hz, CDCl3) delta ppm: 1.38 (3H, t, J = 7.3 Hz), 2.29-2.39 (2H, m), 3.61 (2H, t, J = 6.6 Hz), 4.17 (2H, t, J = 5.9 Hz), 4.35 (2H, q, J = 7.3 Hz), 6.92 (2H, d, J = 8.8 Hz), 8.00 (2H, d, J = 8.8 Hz).

(0067)
(1-2) Sodium hydride (60 % oiliness) 70 mg (1.8 mmol) was suspended in DMF (5 ml), and it was cooled to -15 degrees. To this, DMF (2 ml) solution of 3-hydroxypyridine 170 mg (1.8 mmol) was added dropwise. After stirring for 30 minutes, DMF (3 ml) solution of compound 500 mg (1.8 mmol) of step (1-1) was added dropwise. It was stirred for five hours, and thereafter ethyl acetate and water were added into reaction solution. Organic layer was washed with physiological saline, and next dried with anhydrous sodium sulphate and concentrated, and 4-[3-(pyridine-3-yloxy) propoxy] ethyl benzoate 0.5 g (yield 95 %) was obtained as white solid.
1H NMR (270 M Hz, CDCl3) delta ppm: 1.38 (3H, t, J = 7.3 Hz), 2.26-2.88 (2H, m), 4.19-4.25 (4H, m), 4.34 (2H, q, J = 7.3 Hz), 6.94 (2H, d, J = 9.5 Hz), 7.20-7.22 (2H, m), 8.00 (2H, d, J = 8.8 Hz), 8.21-8.23 (1H, m), 8.33 (1H, br. s).

(0068)
(1-3) Compound 460 mg of Step (1-2) (1.5 mmol) was dissolved in methanol 4 ml. To this, lithium hydroxide 67 mg (1.6 mmol) aqueous solution (2 ml) was added and was reacted at 50 degrees for five hours. After concentration, the reaction liquor was neutralised with dilute hydrochloric acid aqueous solution (pH 5). Precipitated white solid was recovered by

filtration, and 4-[3-(pyridine-3-yloxy) propoxy] benzoic acid 350 mg (yield 83 %) was obtained.

1H NMR (270 M Hz, DMSO-d6) delta ppm: 2.19-2.24 (2H, m), 4.19-4.24 (4H, m), 7.03 (2H, d, J = 8.8 Hz), 7.29-7.43 (2H, m), 7.88 (2H, d, J = 8.8 Hz), 8.16 (1H, d, J = 4.4 Hz), 8.30 (1H, d, J = 2.9 Hz).

(0069)

(1-4) 1N sodium hydroxide aqueous solution (500 ml) was added to dioxane (1000 ml) solution of o-phenylenediamine 108 g (1.0 mol), and dioxane (500 ml) solution of di-t-butyl dicarbonate 218 g (1.1 mol) was added under ice cooling. It was stirred at room temperature for six hours, thereafter was left to stand overnight. The solvent was concentrated to 1/2 vol, and thereafter it was extracted with ethyl acetate. Organic layer was washed with saturated aqueous sodium chloride solution, and dried and solvent was eliminated by distillation, and next thereby obtained residue was refined by silica gel column chromatography (solvent, chloroform), and N-t-butoxycarbonyl-o-phenylenediamine 68.4 g (yield 32 %) were obtained as white solid by washing obtained solid with ethyl ether.

1H NMR (270 M Hz, CDCl3) delta ppm: 1.51 (9H, s), 3.75 (2H, s), 6.26 (1H, s), 6.77 (1H, d, J = 8.1 Hz), 6.79 (1H, dd, J = 7.3, 8.1 Hz), 7.00 (1H, dd, J = 7.3, 8.1 Hz), 7.27 (1H, d, J = 8.1 Hz).

(0070)

(1-5) P-nitrobenzenesulphonyl chloride 140 mg was added to acetonitrile (5 ml) solution of compound of step (1-3) 170 mg (0.6 mmol), triethylamine 0.15 ml, 4-dimethylaminopyridine 13 mg and it was stirred for 20 minutes. To this, compound of step (1-4) 130 mg was added and stirred for ten hours. The reaction liquor was diluted with chloroform, and thereafter organic layer was washed with saturated aqueous sodium bicarbonate solution. It was dried with anhydrous sodium sulphate, and next concentrated, and furthermore refined by silica gel column chromatography (solvent, ethyl acetate), and N-[2-(N-t-butoxycarbonyl) aminophenyl]-4-[3-(pyridine-3-yloxy) propoxy] benzamide 160 mg (yield 55 %) was obtained as white solid.

1H NMR (270 M Hz, CDCl3) delta ppm: 1.51 (9H, s), 2.28-2.37 (2H, m), 4.20-4.26 (4H, m), 6.89-6.98 (3H, m), 7.11-7.24 (5H, m), 7.75 (1H, dd, J = 1.5, 8.1 Hz), 7.93 (2H, d, J = 8.8 Hz), 8.21-8.24 (1H, m), 8.33-8.34 (1H, m), 9.05 (1H, br. s).

(0071)

(1-6) Compound of step (1-5) 130 mg was dissolved in dioxane 3 ml, and it was cooled to 4 degrees. To this, 4 N hydrochloric acid-dioxane solution 1 ml was added and it was stirred for three hours. Ethyl acetate and saturated aqueous sodium bicarbonate solution were added to the reaction liquor. Organic layer was washed with saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next concentrated, and N-(2-aminophenyl)-4-[3-(pyridine-3-yloxy) propoxy] benzamide 100 mg (quantitative) was obtained as white solid.

Mp. 165-168 degC.

1H NMR (270 M Hz, DMSO-d6) delta ppm: 2.20-2.25 (2H, m), 4.07-4.25 (4H, m), 4.86 (2H, s), 6.56-6.62 (1H, m), 6.76-6.79 (1H, m), 6.93-7.15 (4H, m), 7.30-7.43 (2H, m), 7.96 (2H, d, J = 8.8 Hz), 8.16-8.32 (2H, m), 9.54 (1H, s).

(0072)

Example 2.

Synthesis of N-(2-aminophenyl)-4-[2-(pyridine-3-yloxy) ethoxymethyl] benzamide (Table-1: compound number 2).

(2-1) 3-hydroxypyridine 5 g (52 mmol) was added to DMF (60 ml) suspension of sodium hydride (60 % oiliness) 2.2 g and stirred at 4 degrees for 30 minutes. Bromoacetic acid ethyl ester 5.8 ml (52 mmol) was added to this and was stirred for six hours. The reaction liquor was concentrated, and next, ethyl acetate and water were added, and it was distributed. Organic layer was washed with saturated aqueous sodium chloride solution, and next it was dried with anhydrous sodium sulphate. This was concentrated and was refined by silica gel column chromatography (solvent, ethyl acetate), and 4.3 g of (pyridine-3-yloxy) ethyl acetate (yield 45 %) was obtained as an oily substance.

1H NMR (270 MHz, CDCl3) delta ppm: 1.30 (3H, t, J = 7.3 Hz), 4.28 (2H, q, J = 7.3 Hz), 4.67 (2H, s), 7.18-7.24 (2H, m), 8.27-8.35 (2H, m).

(0073)

(2-2) THF (20 ml) suspension of lithium aluminium hydride 0.5 g (13 mmol) was cooled to -78 degrees, and compound of step (2-1) 1.2 g (6.6 mmol) was added. It was stirred for three hours and thereafter water was added and stirred. The insolubles were eliminated by

filtration, and thereafter it was concentrated, and 2-(pyridine-3-yloxy) ethanol 0.8 g (yield 86 %) was obtained.
1H NMR (270 MHz, CDCl3) delta ppm: 4.00 (2H, t, J = 4.4 Hz), 4.14 (2H, t, J = 4.4 Hz), 7.22-7.27 (2H, m), 8.23 (1H, t, J = 2.9 Hz), 8.32-8.36 (1H, m).

(0074)
(2-3) DMF (3 ml) suspension of sodium hydride (60 % oiliness) 30 mg was cooled to 4 degrees, and compound of step (2-2) 100 mg (0.7 mmol) was added. It was returned to room temperature, stirred for 30 minutes, and thereafter cooled to 4 degrees again. 4-bromomethyl benzoic acid methyl ester was added to this and it was reacted at room temperature for five hours. The reaction liquor was concentrated, and next, distributed between ethyl acetate and water. Organic layer was washed with physiological saline, and next dried with anhydrous magnesium sulphate, and concentrated. This was refined with silica gel column chromatography (solvent, ethyl acetate), and 4-[2-(pyridine-3-yloxy) ethoxymethyl] methyl benzoate 88 mg (quantitative) was obtained.
1H NMR (270 MHz, CDCl3) delta ppm: 3.86-3.89 (2H, m), 3.92 (3H, s), 4.20-4.24 (2H, m), 4.69 (2H, s), 7.18-7.26 (2H, m), 7.43 (2H, d, J = 8.8 Hz), 8.03 (2H, d, J = 8.1 Hz), 8.22-8.25 (1H, m), 8.34-8.36 (1H, m).

(0075)
(2-4) Compound 80 mg of step (2-3) (0.3 mmol) was dissolved in methanol 0.5 ml, and aqueous solution (0.3 ml) of lithium hydroxide 13 mg (0.3 mmol) was added. It was stirred for six hours, and thereafter the reaction liquor was concentrated. Concentrate was suspended in dichloromethane 4 ml, and oxalyl chloride 0.1 ml were added and were stirred for two hours. Furthermore toluene was added, and it formed into an azeotrope two times after concentration with reaction solution. Dichloromethane 3 ml were added to this and furthermore dichloromethane (2 ml) solution of compound 100 mg (0.48 mmol) and pyridine 0.4 ml of step (1-4) of Example 1 was added and was stirred for one hour. Ethyl acetate and water were added to the reaction liquor, and it was distributed. Organic layer was washed with physiological saline, and next dried with anhydrous sodium sulphate. After concentration, it was refined using silica gel column chromatography (solvent, ethyl acetate), and N-[2-(N-t-butoxycarbonyl) aminophenyl]-4-[2-(pyridine-3-yloxy) ethoxymethyl] benzamide 122 mg (yield 97 %) was obtained as the pale yellow solid.

1H NMR (270 MHz, CDCl3) delta ppm: 1.51 (9H, s), 3.86-3.90 (2H, m), 4.21-4.24 (2H, m), 4.70 (2H, s), 6.88 (1H, m), 7.13-7.26 (6H, m), 7.46 (2H, d, J = 7.9 Hz), 7.79-7.82 (1H, m), 7.95 (2H, d, J = 8.2 Hz), 8.22-8.24 (1H, m), 8.34 (1H, m), 9.18 (1H, br. s).

(0076)
(2-5) Dichloromethane (1 ml) solution of compound of step (2-4) 110 mg (0.23 mmol) was cooled to 4 degrees, and 10 % trifluoroacetic acid-dichloromethane solution 1 ml was added and stirred for four hours. Saturated aqueous sodium bicarbonate solution and ethyl acetate were added into reaction solution, and it was distributed. Organic layer was washed with physiological saline, and next dried with anhydrous sodium sulphate, concentrated, and N-(2-aminophenyl)-4-[2-(pyridine-3-yloxy) ethoxymethyl] benzamide 88 mg (quantitative) was obtained as the pale yellow solid.
Mp. 112-114 degC.
1H NMR (270 MHz, CDCl3) delta ppm: 3.96-3.90 (2H, m), 4.21-4.24 (2H, m), 4.70 (2H, s), 6.78-6.87 (2H, m), 7.21-7.36 (4H, m), 7.47 (2H, d, J = 8.6 Hz), 7.89 (2H, d, J = 8.2 Hz), 7.95 (1H, br. s), 8.21-8.24 (1H, m), 8.31-8.33 (1H, m).

(0077)
Example 3.
Synthesis of N-(2-aminophenyl)-4-{[2-(pyridine-3-yloxy)-ethylamino] methyl} benzamide (Table-1: compound number 3).

(3-1) DBU 0.98 ml (6.6 mmol) was added to xylene (6 ml) suspension of compound of step (2-1) of Example 2 0.59 g (3.3 mmol) and 4-aminomethyl methyl benzoate 0.60 g (3.0 mmol), and it was heated with stirring at 80 degrees for three hours. Ethyl acetate 50 ml was added to this. It was washed with addition of saturated aqueous sodium bicarbonate solution 10 ml, and thereafter it was washed with saturated aqueous sodium chloride solution 10 ml, and organic layer was dried with anhydrous sodium sulphate and concentrated. Methanol and diisopropyl ether were added to this, and the precipitated solid was recovered by filtration, and 4-{[2-(pyridine-3-yloxy) acetylamino] methyl} benzoic acid methyl ester was obtained 0.65 g (yield 72 %) by drying.
1H NMR (270 MHz, CDCl3) delta ppm: 3.91 (3H, s), 4.61 (2H, s), 4.62 (2H, d, J = 5.1 Hz), 7.00 (1H, s), 7.17-7.30 (2H, m), 7.35 (2H, d, J = 8.8 Hz), 8.01 (2H, d, J = 8.1 Hz), 8.31 (1H, dd, J = 1.5, 4.4 Hz), 8.35 (1H, d, J = 2.9 Hz).

(0078)

(3-2) Borane-dimethylsulphide complex 0.44 ml (4.8 mmol) was added to THF solution of compound of step (3-1) 0.6 g (2 mmol) and it was heated under reflux for four hours. Ten drops of concentrated hydrochoric acid was added to the reaction liquor and stirred at 40 degrees for three hours. The reaction liquor was concentrated, and next, ethyl acetate and saturated aqueous sodium bicarbonate solution were added, and it was distributed. Organic layer was washed with saturated aqueous sodium chloride solution, and next it was dried with anhydrous sodium sulphate, and concentrated. Concentrate was refined by silica gel column chromatography (solvent, ethyl acetate : methanol = 10:1), and 4-{[2-(pyridine-3-yloxy) ethylamino] methyl} methyl benzoate 0.37 g (yield 64 %) were obtained as a colourless oily substance.

1H NMR (270 MHz, CDCl3) delta ppm: 3.04 (2H, t, J = 4.9 Hz), 3.91 (3H, s), 3.94 (2H, s), 4.13 (2H, t, J = 5.3 Hz), 7.16-7.24 (2H, m), 7.43 (2H, d, J = 8.6 Hz), 8.01 (2H, d, J = 8.2 Hz), 8.21-8.23 (1H, m), 8.31-8.32 (1H, m).

(0079)

(3-3) 3N sodium hydroxide aqueous solution 0.5 ml was added to dioxane (10 ml)-water (5 ml) solution of compound of step (3-2) 0.36 g (1.25 mmol). Di-t-butyl di carbonate 330 mg (1.5 mmol) was added under ice cooling. It was returned to room temperature and was stirred for two hours, and thereafter ethyl acetate and physiological saline were added to the reaction liquor, and it was distributed. Organic layer was washed with physiological saline, and thereafter it was dried with anhydrous sodium sulphate. After concentration, it was refined by silica gel column chromatography (solvent, ethyl acetate), and 4-{t-butoxycarbonyl-[2-(pyridine-3-yloxy) ethylamino] methyl} methyl benzoate 0.45 g (yield 93 %) was obtained.

1H NMR (270 MHz, CDCl3) delta ppm: 1.41 (major 9H, s), 1.51 (minor 9H, s), 3.57 (minor 2H, br. s), 3.67 (major 2H, br. s), 3.92 (3H, s), 4.08 (minor 2H, br. s), 4.17 (major 2H, br. s), 4.61 (2H, s), 7.14-7.23 (2H, m), 7.31 (2H, br. s), 7.98-8.01 (2H, m), 8.21-8.26 (2H, m). Mixture of rotational isomer.

(0080)

(3-4) Aqueous solution (2 ml) of lithium hydroxide 50 mg (1.2 mmol) was added to methanol (4 ml) solution of compound of step (3-3) 0.45 g (1.1 mmol) and was stirred at 60 degC for

two hours. It was cooled to room temperature, and next, neutralised with dilute hydrochloric acid (pH 4). The reaction liquor was concentrated, and next, ethyl acetate and saturated aqueous sodium chloride solution were added, and it was distributed. Organic layer was dried with anhydrous sodium sulphate, and next concentrated. Concentrate was dissolved in acetonitrile 10 ml, and triethylamine 0.33 ml, 4-dimethylaminopyridine 26 mg were added. Furthermore p-nitrobenzenesulphonyl chloride 0.26 g was added and stirred for 30 minutes. Compound 0.25 g of step (1-4) of Example 1 (1.2 mmol) was added to this and it was stirred for three hours. The reaction liquor was concentrated, and thereafter ethyl acetate and saturated aqueous sodium bicarbonate solution were added, and it was distributed. Organic layer was washed with saturated aqueous sodium chloride solution, and next dried with anhydrous sodium sulphate. After concentration, it was refined by silica gel column chromatography (solvent, ethyl acetate), and N-[2-(N-t-butoxycarbonyl) aminophenyl]-4-{t-butoxycarbonyl-[2-(pyridine-3-yloxy) ethylamino] methyl} benzamide 0.34 g (yield 56 %) was obtained as white solid.
1H NMR (270 MHz, CDCl3) delta ppm: 1.50 (18H, s), 3.57 (minor 2H, br. s), 3.67 (major 2H, br. s), 4.07-4.23 (2H, m), 4.62 (2H, s), 7.12-7.32 (8H, m), 7.79 (1H, m), 7.90 (2H, d, J = 8.2 Hz), 8.20-8.22 (2H, m), 9.18 (1H, br. s). Mixture of rotational isomer.

(0081)
(3-5) 4 N hydrochloric acid-dioxane 2 ml was added to dioxane (5 ml) solution of compound of step (3-4) 0.33 g (0.58 mmol) and was stirred for two hours. Ethyl acetate and saturated aqueous sodium bicarbonate solution were added to the reaction solution, and it was distributed. Organic layer was washed with saturated aqueous sodium chloride solution, and next dried with anhydrous sodium sulphate and concentrated, and N-(aminophenyl)-4-{[2-(pyridine-3-yloxy) ethylamino] methyl} benzamide 0.21 g (quantitative) was obtained.
Mp. (amorphous).
1H NMR (270 MHz, CDCl3) delta ppm: 3.04 (2H, t, J = 4.9 Hz), 3.95 (2H, s), 4.13 (2H, t, J = 4.6 Hz), 6.81-6.86 (2H, m), 7.06-7.11 (1H, m), 7.19-7.33 (3H, m), 7.46 (2H, d, J = 8.2 Hz), 7.86 (2H, d, J = 7.9 Hz), 8.20-8.22 (1H, m), 8.28-8.29 (1H, m).

The compounds of Example 4 to Example 8 were synthesised in accordance with the same process as in Example 3. Below melting point (mp.) of the compound, measured value of 1H NMR are shown.

(0082)
Example 4.
N-(2-aminophenyl)-4-[(3-pyridine-3-yl-propylamino) methyl] benzamide hydrochloride (hydrochloride of Table-1: compound number 4).
Mp. 192 degC (dec.).
1H NMR (270 MHz, DMSO-d6) delta ppm: 2.13 (2H, t, J = 7.3 Hz), 2.95-2.98 (4H, m), 4.23 (2H, s), 7.30-7.42 (2H, m), 7.49-7.52 (1H, m), 7.61-7.64 (1H, m), 7.78 (2H, d, J = 8.1 Hz), 8.01-8.06 (1H, m), 8.18 (2H, d, J = 8.1 Hz), 8.51-8.54 (1H, m), 8.80-8.91 (2H, m), 9.79 (2H, br. s), 10.63 (1H, s).

(0083)
Example 5.
N-(2-aminophenyl)-4-{[pyridin-3-ylmethyl) amino] methyl} benzamide hydrochloride (hydrochloride of Table-1: compound number 5).
Mp. (amorphous).
1H NMR (270 MHz, DMSO-d6) delta ppm: 4.32 (2H, s), 4.38 (2H, s), 7.30-7.90 (7H, m), 8.15 (2H, d, J = 8.0 Hz), 8.50 (2H, d, J = 8.1 Hz), 8.82 (1H, d, J = 1.5 Hz), 8.99 (1H, s), 10.16 (2H, br. s), 10.56 (1H, s).

(0084)
Example 6.
N-(2-aminophenyl)-4-{[pyridin-2-ylmethyl) amino] methyl} benzamide hydrochloride (hydrochloride of Table-1: compound number 6).
Mp. (amorphous).
1H NMR (270 MHz, DMSO-d6) delta ppm: 4.33 (4H, s), 7.32-7.45 (2H, m), 7.45-7.50 (2H, m), 7.60 (2H, d, J = 7.3 Hz), 7.73 (2H, d, J = 8.1 Hz), 7.93 (1H, ddd, J = 1.5, 7.3, 6.6 Hz), 8.19 (2H, d, J = 8.1 Hz), 9.90 (2H, br. s), 10.64 (1H, br. s).

(0085)
Example 7.
N-(2-aminophenyl)-4-[(methyl-pyridyn-3ylmethylamino) methyl] benzamide hydrochloride (hydrochloride of Table-1: compound number 7).
Mp. (amorphous).

1H NMR (270 MHz, DMSO-d6) delta ppm: 2.60 (3H, s), 4.40-4.80 (4H, m), 7.36 (1H, dd, J = 7.3, 8.1 Hz), 7.44 (1H, dd, J = 6.6, 7.3 Hz), 7.63 (1H, d, J = 6.6 Hz), 7.84 (2H, d, J = 8.1 Hz), 7.54 (1H, d, J = 7.3 Hz), 7.98 (1H, dd, J = 5.1, 7.3 Hz), 8.22 (2H, d, J = 8.1 Hz), 8.72 (1H, d, J = 8.1 Hz), 8.93 (1H, d, J = 5.1 Hz), 9.14 (1H, s), 10.7 (1H, s).

(0086)
Example 8.
N-(2-aminophenyl)-4-[(bis-pyridyn-3-ylmethylamino) methyl] benzamide hydrochloride (hydrochloride of Table-1: compound number 8).
Mp. (amorphous).
1H NMR (270 MHz, DMSO-d6) delta ppm: 4.06 (2H, br. s), 4.31 (4H, br. s), 7.30-7.40 (2H, m), 7.50-7.65 (3H, m), 7.70-7.80 (2H, m), 7.85-7.95 (2H, m), 8.05 (2H, d, J = 5.1 Hz), 8.20-8.35 (2H, m), 8.78 (2H, d, J = 5.1 Hz), 10.53 (1H, br. s).

(0087)
Pharmacological test example 1.
The differentiation induction action test with respect to A2780 cell.
Rise of alkaline phosphatase (ALP) activity is known as indicator of differentiation of human colon cancer cell, and for example sodium butyrate is known to increase ALP activity [Young et al.; Cancer Res., 45, 2976 (1985), Morita et al.; Cancer Res., 42, 4540 (1982)]. So the evaluation of differentiation induction action was carried out with ALP activity as indicator.

(Experiment process)
A2780 cell was inoculated to 96 well plate by 0.1 ml so as to comprise 15,000 cells/well, and on the next day, solution of the test drug which was made serial dilution with culture medium was added by 0.1 ml. It was cultured for three days, and next, cells on plate were washed twice with TBS buffer (20 mM Tris, 137 mM NaCl, pH 7.6). Thereafter, p-nitrophenyl phosphate (9.6 % diethanolamine, 0.5 mM MgCl) solution of concentration of 0.6 mg/ml was added in an amount of by 0.05 ml, and it was incubated at room temperature for 30 minutes. Reaction was stopped by 3N sodium hydroxide aqueous solution 0.05 ml, and thereafter an absorbance of 405 nm was measured, and minimum concentration of drug that induced the increase of ALP activity (ALPmin) was determined.

(Experimental result)
Experimental results are shown in Table-2 (Table 11).

(0088)
Table-2
The differentiation induction action with respect to A2780 cell.

Test compound	ALPmin (μM)
Compound of Example 1	0.03
Compound of Example 2	1
Compound of Example 3	0.3
Compound of Example 4	10
Compound of Example 5	10
Compound of Example 6	10
Compound of Example 7	3
Compound of Example 8	1

(0089)
Advantages Afforded by this Invention.
Novel benzamides of this invention has differentiation induction action and is useful as drug such as therapy and/or improvement drug for malignant tumour, autoimmune disease, dermatopathia, parasite infestation. In particular, the effect as carcinostatic is high and effective in hematopoietic organ tumour, solid cancer.

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